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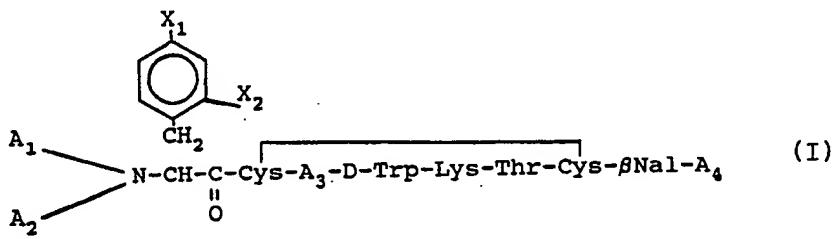


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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :  C07K 7/26, A61K 37/02	A1	(11) International Publication Number: WO 91/09056  (43) International Publication Date: 27 June 1991 (27.06.91)
(21) International Application Number: PCT/US90/07074  (22) International Filing Date: 4 December 1990 (04.12.90)		(74) Agent: CLARK, Paul, T.; Fish & Richardson, One Financial Center, Suite 2500, Boston, MA 02111-2658 (US).
(30) Priority data: 447,876 8 December 1989 (08.12.89) US		(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent).
(71) Applicant: THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND [-/US]; 1430 Tulane Avenue, New Orleans, LA 70115 (US).  (72) Inventors: COY, David, H. ; 4319 Perrier Street, New Orleans, LA 70115 (US). MURPHY, William, A. ; 107 N. Magnolia Drive, Covington, LA 70433 (US).		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: OCTAPEPTIDE ANALOGS OF SOMATOSTATIN HAVING THREONINE AT THE SIXTH POSITION



(57) Abstract

A compound of formula (I), wherein each A<sub>1</sub> and A<sub>2</sub>, independently, is H C<sub>1-12</sub> alkyl, C<sub>7-10</sub> phenylalkyl, R<sub>1</sub>CO (where R<sub>1</sub> is C<sub>1-20</sub> alkyl, C<sub>3-20</sub> alkenyl, C<sub>3-20</sub> alkenyl, phenyl, naphthyl, or C<sub>7-10</sub> phenylalkyl), or R<sub>2</sub>OCO (where R is C<sub>1-10</sub> alkyl or C<sub>7-10</sub> phenylalkyl), provided that when one of A<sub>1</sub> or A<sub>2</sub> is R<sub>1</sub>CO or R<sub>2</sub>OCO, the other must be H; each X<sub>1</sub> and X<sub>2</sub>, independently, is H, F, Cl, Br, OH, CH<sub>3</sub>, or CF<sub>3</sub>, provided that at least one of X<sub>1</sub> and X<sub>2</sub> must be H; A<sub>3</sub> is Phe or Tyr; and A<sub>4</sub> is OH, NH<sub>2</sub>, or NH-R<sub>3</sub> (wherein R<sub>3</sub> is a saturated aliphatic C<sub>1-8</sub> alkyl); or a pharmaceutically acceptable salt thereof; a therapeutic composition comprising such compound; and a method of using such compound.

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OCTAPEPTIDE ANALOGS OF SOMATOSTATIN  
HAVING THREONINE AT THE SIXTH POSITION

Background of the Invention

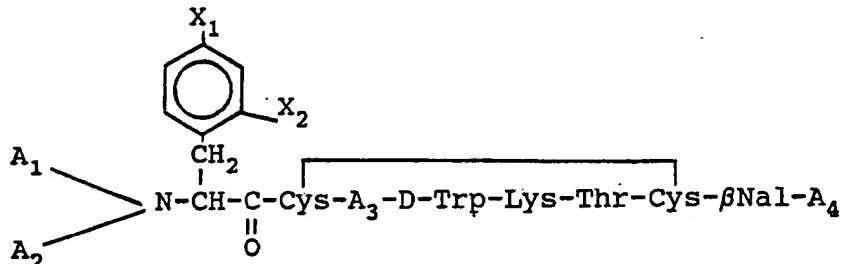
This invention relates to therapeutic peptides.

5        A number of somatostatin analogs exhibiting growth  
hormone-release-inhibiting activity have been described  
in the literature, including analogs containing fewer  
than the naturally-occurring fourteen amino acids. For  
example, Coy et al., U.S. Patent No. 4,485,101, hereby  
10      incorporated by reference, describes dodecapeptides  
having an amino-terminal acetyl group, a carboxy-terminal  
amino group, D-Trp at position 6, and p-Cl-Phe at  
position 4. (The name of each amino acid is herein  
designated by its standard three-letter abbreviation; the  
15      stereoisomeric designation of each amino acid is L unless  
otherwise specified.)

Summary of the Invention

In general, the invention features a compound of  
the formula:

20



25

wherein

each A<sub>1</sub> and A<sub>2</sub>, independently, is H C<sub>1-12</sub> alkyl,  
C<sub>7-10</sub> phenylalkyl, R<sub>1</sub>CO (where R<sub>1</sub> is C<sub>1-20</sub>  
alkyl, C<sub>3-20</sub> alkenyl, C<sub>3-20</sub> alkenyl, phenyl,  
naphthyl, or C<sub>7-10</sub> phenylalkyl), or R<sub>2</sub>OCO (where  
R is C<sub>1-10</sub> alkyl or C<sub>7-10</sub> phenylalkyl),  
30      provided that when one of A<sub>1</sub> or A<sub>2</sub> is R<sub>1</sub>CO or  
R<sub>2</sub>OCO, the other must be H;

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each  $X_1$  and  $X_2$ , independently, is H, F, Cl, Br, OH,  $\text{CH}_3$ , or  $\text{CF}_3$ , provided that at least one of  $X_1$  and  $X_2$  must be H;

5      $A_3$  is Phe or Tyr; and

5      $A_4$  is OH,  $\text{NH}_2$ , or  $\text{NH}-R_3$  (wherein  $R_3$  is a saturated aliphatic  $C_{1-8}$  alkyl):

or a pharmaceutically acceptable salt thereof. The naturally-occurring amino acids are indicated by their generally-accepted three-letter symbols; unless the D-10 stereoisomer of an amino acid (other than  $\beta\text{Nal}$ ) is specified, the L-form is assumed. " $\beta\text{Nal}$ " denotes D- or L- $\beta$ -naphthylalanine, unless the D- or L- stereoisomer is specified.

In preferred embodiments, each  $A_1$  and  $A_2$ , 15 independently, is H or a saturated aliphatic  $C_{1-3}$  alkyl; each  $X_1$  and  $X_2$ , independently, is H, F, Cl, or OH, provided that at least one of  $X_1$  and  $X_2$  must be H; and  $R_3$  is saturated aliphatic  $C_{1-3}$  alkyl; more preferably, the compound has the formula:

20    D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys- $\beta\text{Nal-NH}_2$   
  or  
  D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys- $\beta\text{Nal-NH}_2$

In another aspect, the invention features compounds of the formula:

25    D- $\beta\text{Nal-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH}_2$   
  and  
  D- $\beta\text{Nal-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH}_2$   
  or a pharmaceutically acceptable salt thereof.

Also featured is a combination of one of the above 30 compounds and a pharmaceutically acceptable carrier

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substance in a therapeutic composition capable of inhibiting the release of growth hormone ("GH"), epidermal growth factor, insulin, glucagon, pancreatic exocrine secretions, or substance P, and preferably of  
5 GH.

In preferred embodiments, the composition is in the form of a pill, tablet, capsule, or liquid for oral administration; a cream, gel, lotion, spray or ointment for application to the skin of a patient; a liquid  
10 capable of being administered nasally as drops or spray; or a liquid capable of intravenous, subcutaneous, parenteral, or intraperitoneal administration. The therapeutic composition can also be in the form of an oil emulsion or dispersion in conjunction with a lipophilic  
15 salt such as a pamoic acid, or in the form of a biodegradable sustained-release formulation for subcutaneous or intramuscular administration. For maximum efficacy, zero-order release is desired. Zero-order release can be obtained using an implantable or  
20 external pump to administer the therapeutic composition.

The compounds of the invention exhibit a broad range of biological activities related to their antisecretory and antiproliferative properties. The compounds suppress the secretion of several endocrine  
25 hormones, including insulin, glucagon, and, in particular, growth hormone (GH). The compounds of the invention also suppress pancreatic and gastric exocrine secretions, and suppress or modulate the release of some neurotransmitters, including substance P and  
30 acetylcholine.

The somatostatin analogs can effect tumor cell multiplication by preventing the release of mitotic factors (such as insulin-like growth factor 1 (IGF-1), gastrin-releasing peptides, etc.), and may interfere with  
35 the intracellular transduction mechanism, as, for

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example, in the case of epidermal growth factor (EGF)-induced cell proliferation.

The aromatic lipophilic N-terminal end can provide long-lasting in vivo activity.

5 Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Description of the Preferred Embodiments

Structure

10 The compounds of the invention, which are peptide analogs of somatostatin, have the general formula recited in the Summary of the Invention, above.

The compounds can be provided in the form of pharmaceutically acceptable salts or complexes. As used herein, the term "pharmaceutically acceptable salts or complexes" refers to salts or complexes that retain the desired biological activity of the parent compound and do not impart any undesired toxicological effects. Examples of such salts are (a) acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acids, naphthalenedisulfonic acids, and polygalacturonic acid; (b) base addition salts formed with polyvalent metal cations such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium, and the like, or with an organic cation formed from N,N-dibenzylethylene-diamine or ethylenediamine; or (c) combinations of (a) and (b): e.g., a zinc tannate salt or the like.

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Synthesis

The synthesis of one octapeptide follows. Other compounds of the invention can be prepared by making appropriate modifications, within the ability of someone 5 or ordinary skill in this field, or the following synthetic method.

The first step in the preparation of D-Phe-Cys-Phe-D-Trp-Lys-Val-Cys- $\beta$ Nal-NH<sub>2</sub>, was the preparation of the intermediate tert-butyloxycarbonyl-D-10 Phe-S-methylbenzyl-Cys-Phe-D-Trp-N<sup>E</sup>-benzyloxycarbonyl-Lys-Thr-S-methylbenzyl-Cys- $\beta$ Nal-NH<sub>2</sub>-benzyhydrylamine resin, as follows.

Methyl-benzyhydrylamine-polystyrene resin (Advanced Chem-Tech, Inc.) in the chloride ion form was placed in the reaction vessel of a Beckman 990B peptide synthesizer programmed to perform the following reaction cycle: (a) methylene chloride; (b) 33% trifluoroacetic acid in methylene chloride (2 times for 1 and 25 min each); (c) methylene chloride; (d) ethanol; (e) methylene 20 chloride; (f) 10% triethylamine in chloroform.

The neutralized resin was stirred with Boc- $\beta$ Nal and disopropylcarbodiimide (1.5 mmole each) in methylene chloride for 1 h and the resulting amino acid resin was then cycled through steps (a) to (f) in the above wash 25 program. The following amino acids (1.5 mmole) were then coupled successively by the same procedure: Boc-S-methylbenzyl-Cys, Boc-Thr, Boc-N<sup>E</sup>-benzyloxycarbonyl-Lysine, Boc-D-trp, Boc-Phe, Boc-S-methylbenzol-Cys, Boc-D-Phe.

30 The resin was washed and dried and then mixed with anisole (4 ml) and anhydrous hydrogen fluoride (36 ml) at 0°C and stirred for 45 min. (one can also use thioanisole, trifluoroacetic acid, and trifluoromethane sulfonic acid at a ration of 1:90:9, for 6 h). Excess 35 hydrogen fluoride was evaporated rapidly under a stream

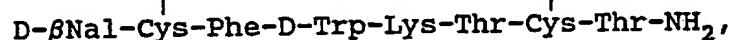
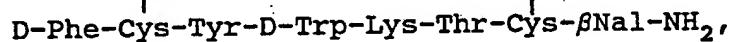
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of dry nitrogen and free peptide precipitated and washed with ether. The crude peptide was then dissolved in 800 ml of 90% acetic acid, to which was added I<sub>2</sub> in methanol until a permanent brown color was present. The solution 5 was then stirred for 1 h before removing the solvent in vacuo. The resulting oil was dissolved in a minimum volume of 50% acetic acid and eluted on a column (2.5 X 100 mm) of Sephadex G-25. Fractions containing a major component by UV absorption and thin-layer chromatography 10 were then pooled, evaporated to a small volume, and applied to a column (2.5 X 50 cm) or Vydac octadecylsilane (10-15  $\mu$ M).

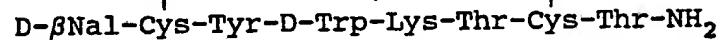
The column was eluted with a linear gradient of 10-50% acetonitrile in 0.1% trifluoroacetic acid in 15 water. Fractions were examined by thin-layer chromatography and analytical high-performance liquid chromatography, pooled to give maximum purity, and, if desired, a different salt prepared, e.g., acetate or phosphate. Repeated lyophilization of the solution from 20 water gave 120 mg of the product as white, fluffy powder.

The product was found to be homogeneous by high-performance liquid chromatography and thin-layer chromatography. Amino acid analysis of an acid hydrolysate confirmed the composition of the octapeptide.

25 Compounds of the invention having the formulas



and



30 were made according to methods analogous to those described above.

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Use

When administered to mammals, particularly humans (e.g. orally; topically; intravenously; parenterally in a sustained release, biodegradable form; nasally; or by suppository), the compounds can be effective to inhibit the secretion of various hormones and trophic factors. They may be used to suppress certain endocrine secretions, such as GH, insulin, glucagon and prolactin, the treatment of, for example, acromegaly; endocrine tumors such as carcinoids, vipomas, insulinomas, and glucagonomas; or diabetes and diabetes-related pathologies, including retinopathy, nephropathy, dawn syndrome and type 2 diabetes. The compounds may also be used to suppress exocrine secretions in the pancreas, stomach and intestines, for treatment of, for example, pancreatitis, fistulas, bleeding ulcers, and diarrhea associated with such diseases as AIDS or cholera. Disorders involving autocrine or paracrine secretions of trophic factors such as IGF-1 (as well as some endocrine factors) which may be treated by administration of these compounds include cancers of the breast, prostate, and lung (both small cell and non-small cell epidermoids) as well as hepatomas, neuroblastomas, colon and pancreatic adenocarcinomas (ductal type), chondrosarcomas, and melanomas, and also atherosclerosis associated with vascular grafts and restenosis following angioplasty.

The compounds of the invention also are useful to suppress the mediators of neurogenic inflammation (e.g., substance P or the tachykinins), and thus may be used in the treatment of such pathologies as the rheumatoid arthritis; psoriasis; topical inflammation such as is associated with sunburn, eczema, or other sources of itching; and allergies, including asthma. The compounds also can function as neuromodulators in the central nervous system, with useful applications in the treatment

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of Alzheimer's disease and other forms of dementia, pain (as a spinal analgesic), and headaches. Furthermore, in disorders involving the splanchnic blood flow, including cirrhosis, oesophageal varices, and certain cases of 5 mushroom poisoning, the compounds of the invention can provide cytoprotection.

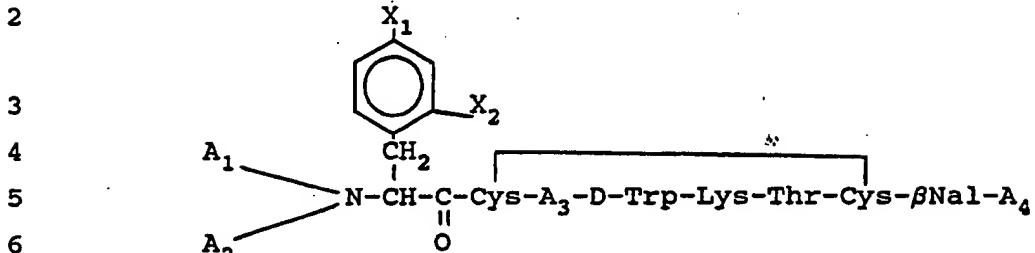
The compounds can be administered to a mammal, e.g., a human, in a dosage of 0.01 to 50 mg/kg/day, preferably 0.1 to 5 mg/kg/day.

10 Other embodiments are within the following claims.

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Claims

1       1. A compound of the formula:



wherein

each  $A_1$  and  $A_2$ , independently, is H  $C_{1-12}$  alkyl,  
 $C_{7-10}$  phenylalkyl,  $R_1CO$  (where  $R_1$  is  $C_{1-20}$   
alkyl,  $C_{3-20}$  alkenyl,  $C_{3-20}$  alkenyl, phenyl,  
naphytetyl, or  $C_{7-10}$  phenylalkyl), or  $R_2OCO$  (where  
 $R$  is  $C_{1-10}$  alkyl or  $C_{7-10}$  phenylalkyl),  
provided that when one of  $A_1$  or  $A_2$  is  $R_1CO$  or  
 $R_2OCO$ , the other must by H;  
each  $X_1$  and  $X_2$ , independently, is H, F, Cl, Br, OH,  
 $CH_3$ , or  $CF_3$ , provided that at least one of  $X_1$   
and  $X_2$  must be H;  
 $A_3$  is Phe or Tyr; and  
 $A_4$  is OH,  $NH_2$ , or  $NH-R_3$  (wherein  $R_3$  is a saturated  
aliphatic  $C_{1-8}$  alkyl);  
or a pharmaceutically acceptable salt thereof.

1       2. The compound of claim 1, wherein  
2       each  $A_1$  and  $A_2$ , independently, is H of a saturated  
3       aliphatic  $C_{1-3}$  alkyl:

4       each  $X_1$  and  $X_2$ , independently, is H, F, Cl, or  
5       OH, provided that at least one of  $X_1$  and  $X_2$  must  
6       by H; and  
7        $R_3$  is a saturated aliphatic  $C_{1-3}$  alkyl;  
8       or a pharmaceutically acceptable salt thereof.

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1       3. The compound of claim 2, wherein said compound  
2   has the formula:

3                     D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys- $\beta$ Nal-NH<sub>2</sub>,  
4   or a pharmaceutically acceptable salt thereof.

1       4. The compound of claim 2 wherein said compound  
2   has the formula:

3                     D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys- $\beta$ Nal-NH<sub>2</sub>,  
4   or a pharmaceutically acceptable salt thereof.

1       5. A compound of the formula:

2                     D- $\beta$ Nal-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,  
3                     or

4                     D- $\beta$ Nal-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>,  
5   or a pharmaceutically acceptable salt thereof.

1       6. A therapeutic composition capable of  
2   inhibiting the release of GH; epidermal growth factor;  
3   insulin; glucagon; prolactin; exocrine secretions from  
4   the pancreas, stomach or intestines; the tachykinin and  
5   substance P, said composition comprising a  
6   therapeutically effective amount of the compound of claim  
7   1 or claim 5, together with a pharmaceutically acceptable  
8   carrier substance.

1       7. The therapeutic composition of claim 6,  
2   wherein said composition is capable of inhibiting the  
3   release of GH.

1       8. The therapeutic composition of claim 6,  
2   wherein said composition is in the form of a liquid,

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3      pill, tablet, or capsule for oral administration to a  
4      human patient in need of said composition.

1            9. The therapeutic composition of claim 6, said  
2      composition being in the form of a cream, gel, lotion,  
3      spray, or ointment for application to the skin of a human  
4      patient in need of said composition.

1            10. The therapeutic composition of claim 6, said  
2      composition being in the form of a liquid capable of  
3      being administered nasally as drops or spray to a human  
4      patient in need of said composition.

1            11. The therapeutic composition of claim 6, said  
2      composition being in the form of a liquid for  
3      intravenous, subcutaneous, parenteral, or intraperitoneal  
4      administration to a human patient in need of said  
5      composition.

1            12. The therapeutic composition of claim 6, said  
2      composition being in the form of a biodegradable  
3      sustained-release composition for intramuscular  
4      administration to a human patient in need of said  
5      composition.

1            13. The therapeutic composition of claim 6,  
2      wherein said composition includes a lipophilic salt and  
3      is suitable for administration in the form of an oil  
4      emulsion or dispersion to a human patient in need of said  
5      composition.

1            14. A method of treating a mammal in need of  
2      reduction of GH; epidermal growth factor; insulin;  
3      glucagon; prolactin; exocrine secretions from the  
4      pancreas, stomach or intestines; the tachykinins and

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5 substance P, said method comprising administering to said  
6 mammal a therapeutically effective amount of the compound  
7 of claim 1 or claim 5.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US90/07074

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) \*

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5):C07K 7/26; A61K 37/02

U.S. CL.: 530/311, 328, 317; 514/16

## II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System	Classification Symbols
U.S.	530/311, 328, 317; 514/16

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched \*

## III. DOCUMENTS CONSIDERED TO BE RELEVANT \*

Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	US. A. 4,328,135 (SARANTAKIS), 04 May 1982, see the entire document.	1 & 6-14
A	US. A. 4,435,385 (BAUER et al), 06 March 1984, see the entire document.	1 & 6-14
A	US. A. 4,485,101 (COY et al), 27 November 1984, see the entire document.	1 & 6-14
Y	US. A. 4,853,371 (COY et al), 01 August 1989, see col. 1, lines 25-49; col. 2, lines 5-37.	1 & 6-14
Y	Proceedings 9th Annual Peptide Symposium Abstract, issued July 1985, Cai et al., "Synthesis and evaluation of activities of octapeptide analogs of Somatostatin", pp. 627-630, particularly page 628.	1,3 & 6-14

\* Special categories of cited documents: <sup>10</sup>

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

14 March 1991

Date of Mailing of this International Search Report

29 APR 1991

International Searching Authority

ISA/US

Signature of Authorized Officer

T.D. Wessendorf  
T.D. Wessendorf

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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V.  OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE<sup>1</sup>

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1.  Claim numbers \_\_\_\_\_, because they relate to subject matter <sup>12</sup> not required to be searched by this Authority, namely:

2.  Claim numbers \_\_\_\_\_, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out <sup>13</sup>, specifically:

3.  Claim numbers \_\_\_\_\_, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI.  OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING<sup>2</sup>

This International Searching Authority found multiple inventions in this international application as follows:

See attachment

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

1 and 6-14 (First listed specie) Telephone Practice.

4.  As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

The additional search fees were accompanied by applicant's protest.

No protest accompanied the payment of additional search fees.

PCT/US90/07074

Attachment to PCT/ISA/210

This application is directed to a generic inventions containing multiple species.

Applicants are required to elect disclosed specie from the claimed genus. For example, a single definition for each of the given variables like  $A_1$  definition H;  $A_2=H$ ,  $A_3=PHe$ ,  $A_4=OH; X_1=H; X_2=F$ ; etc. or species from claims 3-5.

Each of the species comprised in the genus are distinct since they are physically or structurally dissimilar. One specie in the claimed genus containing specific definitions for each variables would not suggest the other species containing different definitions for the same given variable(s).

In conformance with PCT Rule 13.1, the composition comprising the peptide (specie) and method of using said peptide i.e. claims 6 -14 would be examined with the elected (peptide) specie.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. Wessendorf whose telephone number is (703) 308-3697.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 309-0196.

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